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(54) Title: METAL IMPLANTS

(57) Abstract: A metal implant for use in a surgical procedure is provided with a surface layer that is integral with the metal substrate, and which incorporates a biocidal material. The surface layer is grown by anodising at a voltage between 50 and 150 V, and the biocidal material incorporated in it by ion exchange. This produces a significantly harder surface than anodising at low voltage, and generates pits containing ion-absorbing material.

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Metal Implants

This invention relates to metal implants for use in surgical procedures, and in particular to the 5 introduction of a biocidal material into such implants to suppress or control infection.

Various surgical procedures require the use of implants. For example cancerous bone may be removed, in 10 prosthetic surgery, to be replaced by a metal implant. Such an implant may for example be of titanium alloy, which is very strong and relatively light. To ensure a hard-wearing surface the provision of a titanium nitride coating has been suggested. There is furthermore a risk 15 of introducing infection when implanting such metal implants, and it has been suggested that metallic silver might be electroplated onto metal implants, the silver being a biocidal material that can control infection without causing toxic effects to the patient. However 20 such coatings, whether of titanium nitride or silver, may be undercut due to corrosion from body fluids, so that the coating may detach from the implant, which may can increase wear and cause tissue damage. WO 03/089023 describes a way of pretreating an implant by anodising at 25 10 V to form a phosphate layer, and then incorporating biocidal silver ions in this layer by ion exchange. A way of making a significantly improved layer has now been found.

30 According to the present invention there is provided a method of treating a titanium metal implant for use in a surgical procedure, so as to form a surface layer that is integral with the metal substrate and which incorporates a biocidal material, wherein the method 35 comprises anodising the implant at a voltage above 50 V for a period of at least 30 min, so as to generate a

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surface layer, and then performing ion exchange so as to incorporate ions of a biocidal metal into the surface layer.

5 The biocidal material should preferably be effective for at least 6 weeks, preferably for up to 6 months after surgery, and the release rate should be low to avoid toxic effects on body cells. Furthermore the total quantity of biocidal material is preferably also limited
10 to minimize any toxic effects. Performing the anodising at a voltage above 50 V has two effects: it initially generates a dense hard surface layer whose thickness is primarily determined by the voltage, and it then generates shallow pits in the surface which are filled
15 with a somewhat softer and more porous material. The absorption of biocidal metal ions is primarily into the material within the shallow pits, so that the total quantity of biocidal material and its release rate can be controlled by controlling the magnitude of the anodising
20 voltage and its duration, so as to control the number and size of the shallow pits. The anodising might be carried out at a voltage as high as 500 V or 750 V, but more usually is performed between 50 V and 150 V. The duration may be up to 24 hours, but preferably no more than 12
25 hours, for example 2 hours or 6 hours.

It is also desirable if the surface is highly polished before production of the surface layer. This may for example be achieved by electropolishing. One
30 benefit of performing the anodising at a voltage in this significantly higher range is that the surface finish is not deleteriously affected; if the surface is polished before anodising so as to be shiny, then it will remain shiny after the high-voltage anodising step. This is in
35 contrast to the effect of low voltage anodising, which generates a milky or matt appearance at the surface.

In principle, a range of different materials may be used for the biocidal material. Gold, platinum and palladium would be potentially suitable, although expensive; silver is preferable as it is not particularly 5 soluble in body fluids due to the presence of chloride ions and the low solubility of silver chloride. Other elements such as copper, tin, antimony, lead, bismuth and zinc might be used as ions combined into the surface 10 layer. The rate of release would be controlled, in this case, primarily by the strength of the absorption of the metal ions in the layer.

The term titanium metal implant refers to an implant of a metal that is predominantly titanium, preferably at 15 least 75% titanium by weight. The invention is applicable to prosthetic implants that are made of pure titanium, or a titanium alloy. The standard alloy for this purpose is titanium 90% with 6% aluminium and 4% vanadium (British standard 7252).

20

Preferably the implant is initially polished to provide a very smooth surface. Titanium alloy can be electro-polished using acetic acid, or a mixture of nitric and hydrofluoric acids. Alternatively the implants 25 might be subjected to a combination of anodic passivation with mechanical polishing, which may be referred to as electropolishing, this process removing the oxide that protects surface roughness, the surface at that point then being electrochemically re-passivated, so producing 30 a mirror-smooth finish. Various electrolytes are suitable for this purpose, including nitric acid mixed

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with sulphuric acid, sodium hydroxide, sodium phosphate, or sodium hydroxide mixed with sodium nitrate.

After polishing the surface of the metal, surface conversion can take place. A layer of metal oxide or phosphate is formed by anodising in a suitable electrolyte, so that the oxide or phosphate layer builds up at the surface of the metal, as described above. Biocidal metal ions can then be absorbed from an aqueous salt solution into the oxide or phosphate matrix, for example the ions Ag^+ or Cu^{++} . Cations of palladium, platinum or even ruthenium could be absorbed in a similar way. If desired, deposited silver, platinum or palladium could then be converted to metal within the oxide or phosphate surface coating, this reduction being performed chemically or electrochemically or by light.

The invention will now be further and more particularly described, by way of example only, and with reference to the accompanying drawings in which:

Figure 1 shows a diagrammatic sectional view through part of the surface of an implant subjected to a low voltage anodising treatment;

25

Figure 2 shows a corresponding sectional view of an implant subjected to a high-voltage anodising treatment of the invention; and

30

Figure 3 shows the surface composition profile of a specimen treated as in figure 2, the profile being determined by secondary neutral mass spectrometry.

A hip implant is made of titanium alloy (Ti/Al/V). 35 The implant is cleaned ultrasonically using first acetone as the liquid phase, and then a 1 M aqueous solution of

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sodium hydroxide, and is then rinsed in de-ionised water. The surface is initially shiny, with a pale grey colour. The cleaned implant is then immersed in a stirred 12% (weight) solution of phosphoric acid, and is anodised for 5 2 hours at a maximum voltage of 100 V and a maximum current of 10 mA/cm^2 , so as to form a surface coating of titanium oxide and phosphate. Within a couple of minutes a dense dielectric layer is formed on the surface, and the current then adopts a stable low value for the rest 10 of the anodising period. The surface forms a hard surface layer which can have different coloured appearances due to optical interference effects; during the initial stage of anodising, the surface colour varies from purple/blue, through blue, green, yellow, orange, and then finally 15 red. Anodising at 100 V produces a film thickness of about $0.14 \mu\text{m}$ (140 nm). The anodised implant is then rinsed in de-ionised water again.

The implant is then immersed in a stirred 0.1 M 20 aqueous solution of silver nitrate, and left for 2 hours. As a result of ion exchange there is consequently some silver phosphate in the titanium phosphate coating. The implant is then ready to be implanted. During exposure 25 to body fluids there will be a slow leaching of silver ions from the phosphate layer, so that any bacteria in the immediate vicinity of the implant are killed. Infection arising from the implant is therefore suppressed.

30 Referring to figure 1, where anodising of a titanium implant 30 is performed at 10 V for 2 hours, the current falls to a low value over the first couple of minutes during anodising, but the current then rises again with the formation of a porous surface layer with $20 \mu\text{m}$ 35 macropores and $1 \mu\text{m}$ micropores. This produces a porous high-surface-area layer 32 which is about $2 \mu\text{m}$ thick, of

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hydrous titanium oxide and phosphate. This is highly effective at absorbing silver ions, and can provide an initial silver capacity of about $70-100 \mu\text{g}/\text{cm}^2$; this is well below the toxic level, but more than adequate to 5 provide a biocidal effect.

Referring to figure 2, where anodising is performed at a high voltage such as 100 V for 2 hours, as mentioned above the current initially falls to a low value, and 10 then remains steady. The surface forms a hard anodised oxide layer 34 typically of thickness about 0.14 μm , but in which there are pits 36 typically of diameter about 5 μm and depth about 0.4 μm which are filled with titanium oxide as a result of hydrolysis from localised titanium 15 dissolution. Such pits 36 are approximately circular in plan, and make up between 15 and 20% of the surface area. Surface analysis techniques have confirmed that, after ion exchange treatment, the absorbed silver is associated with the titanium oxide/phosphate phase at the surface; 20 this is true for both the low voltage and the high-voltage anodising procedures. The high-voltage anodised surface absorbs silver to a small extent at the outer surface of the hard layer 34, and to a larger extent within the more porous material in the pits 36; overall 25 there is somewhat less initial capacity for silver, typically about $9 \mu\text{g}/\text{cm}^2$. This is still sufficient to provide the required biocidal effect.

Thus the effects of anodising at 100 V for 2 hours 30 are to produce a hard and compact oxide layer whose thickness depends upon the voltage (the relationship being approximately 1.4 nm per volt) this film having a coloured appearance determined by the film thickness, and retaining the surface microstructure (e.g. polished 35 finish). Furthermore the surface is pitted, with pits about 0.3 μm deep filled with hydrous titanium dioxide

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covering slightly less than a fifth of the surface. This can be loaded with silver at about 9 $\mu\text{g}/\text{cm}^2$.

Measurements of the surface composition at different depths below the surface have been measured using secondary neutral mass spectrometry on a titanium alloy specimen treated as described above. The results are shown in figure 3, to which reference is now made. It will be observed that in the surface region, down to about 0.14 μm (marked by the broken line), the composition is about 73% oxygen and about 18% titanium, with phosphorus at about 6%; this corresponds to the hard surface layer 34. There is then a zone in which the titanium concentration increases and the oxygen concentration decreases, down to about 0.4 μm ; this corresponds to the depths at which there are pits 36 containing titanium oxide. At greater depths the composition is evidently a titanium/aluminium alloy.

Measurements have also been made of the loss of silver from the surface of the anodised implant into a brine flowing over the surface (at a linear velocity of about 0.7 $\text{ml cm}^{-2} \text{h}^{-1}$). The initial rate of silver release over the first 24 hours is about 0.1 $\mu\text{g cm}^{-2} \text{h}^{-1}$, the release rate then gradually falling over the next 24 hours to about half that value, then remaining steady for another 48 hours, before decreasing again. But throughout this period the concentration of silver in the leaching brine was sufficient to be biocidal.

The silver capacity can be adjusted in three ways. It may be changed by changing the number of pits, and this can be either by changing the voltage, or by changing the concentration of pitting agents (such as chloride or fluoride ions) which are present as impurities in the phosphate electrolyte. For example the

concentration of such monovalent ions can be decreased by a selective anion exchange treatment; or their concentration could be increased by adding appropriate acids. For example the concentration of chloride ions 5 might be increased by adding NaCl or hydrochloric acid to the phosphoric acid electrolyte, preferably such that the chloride ion concentration is no more than 500 ppm, more preferably no more than 50 ppm. Alternatively the pits might be grown to larger depths and diameters; this may 10 be achieved by carrying out the anodising for a longer period of time.

It may also be appropriate to change the current density.

15

By anodising at a higher voltage the thickness of the hard oxide layer can be increased, for example being about 0.7 µm at 500 V. Once this layer has been formed, as indicated by the decrease in the current, the voltage 20 might be changed. During this second stage the pits are formed, and gradually grow in size, and this may be carried out at a lower voltage.

It will be appreciated that the invention is also 25 applicable to implants which are at least partly made of porous titanium, as the high-voltage anodising process is effective within the pores. This can lead to significantly higher loading of silver per unit volume of implant, because of the much larger surface area.

30

The electrical connection to the implant, so that anodising can be performed, may for example be through a titanium wire spot-welded onto the implant. Alternatively a blind hole may be drilled into the 35 implant, and electrical connection made by a screw connector in this hole, a sealant (for example silicone)

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preventing electrolyte access to the contact area. Exposed parts of the connector can be protected from anodisation for example by a PTFE insulating tape. After the anodising process, the connector would be removed, 5 and the hole could be filled by a bio-compatible plug, for example of anodised titanium, or of a polymer.

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Claims

1. A method of treating a titanium metal implant for use in a surgical procedure, so as to form a surface layer 5 that is integral with the metal substrate and which incorporates a biocidal material, wherein the method comprises anodising the implant at a voltage above 50 V for a period of at least 30 min, so as to generate a surface layer, and then performing ion exchange so as to 10 incorporate ions of a biocidal metal into the surface layer.
2. A method as claimed in claim 1 wherein the anodising is performed so as to generate a dense hard surface layer 15 and also shallow pits in the surface which are filled with a somewhat softer and more porous material, and wherein the magnitude of the anodising voltage and its duration are controlled, so as to control the number and size of the shallow pits.
3. A method as claimed in claim 1 or claim 2 wherein the 20 biocidal metal is silver.
4. A method as claimed in any one of the preceding 25 claims wherein the anodising step uses an electrolyte comprising phosphoric acid.
5. A method as claimed in claim 4 wherein the phosphoric acid is of concentration between 5% and 20% by weight.
6. A method as claimed in claim 4 or claim 5 wherein the 30 electrolyte comprises chloride ions at a concentration no more than 500 ppm.

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Fig.1.
(Prior art)

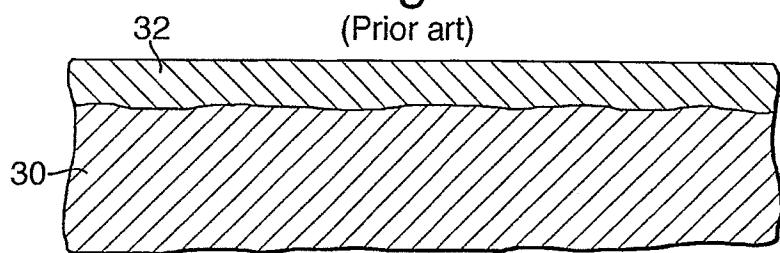


Fig.2.

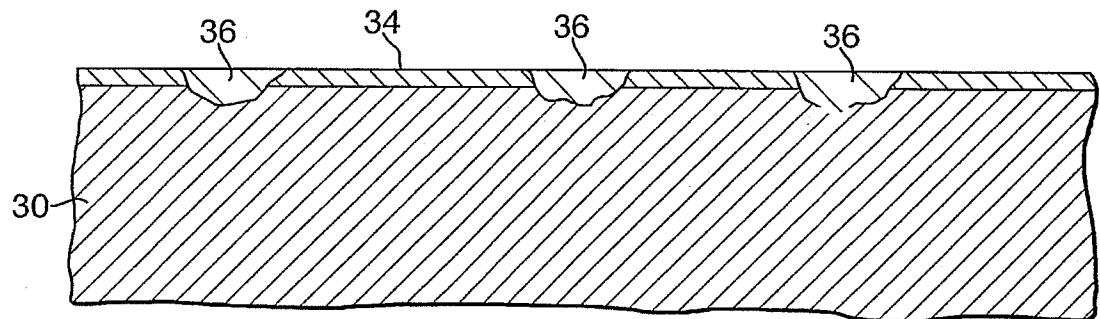
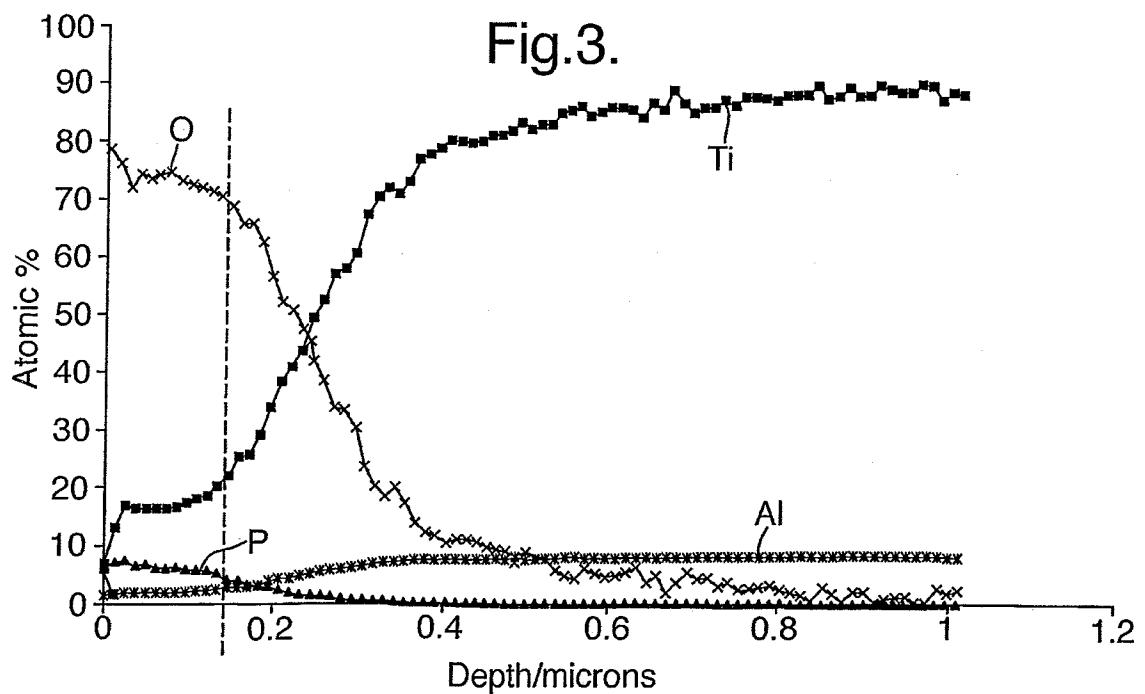


Fig.3.



INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER					
IPC 7 C25D11/26 A61F2/30 A61L27/04 A61L27/06 A61L27/30					
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According to International Patent Classification (IPC) or to both national classification and IPC					
B. FIELDS SEARCHED					
Minimum documentation searched (classification system followed by classification symbols)					
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched					
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)					
EPO-Internal					
C. DOCUMENTS CONSIDERED TO BE RELEVANT					
Category ^a	Citation of document, with indication, where appropriate, of the relevant passages				Relevant to claim No.
Y	<p>WO 03/089023 A (ACCENTUS PLC; PICKFORD, MARTIN, EDWARD, LEE; TURNER, ANDREW, DEREK) 30 October 2003 (2003-10-30) cited in the application page 5, line 1 – line 20; claims</p> <p>-----</p> <p>WO 00/72777 A (NOBEL BIOCARE AB ; HALL, JAN; LAUSMAA, JUKKA) 7 December 2000 (2000-12-07) page 3, line 1 – line 6 page 4, line 19 – line 20 page 8, line 7 – line 11 page 10, line 7 – line 16 page 19, line 6 – line 25</p> <p>-----</p> <p style="text-align: center;">-/-</p>				1-3
Y					1-3
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.			<input checked="" type="checkbox"/> Patent family members are listed in annex.		
<p>^a Special categories of cited documents :</p> <p>*A* document defining the general state of the art which is not considered to be of particular relevance</p> <p>*E* earlier document but published on or after the international filing date</p> <p>*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>*O* document referring to an oral disclosure, use, exhibition or other means</p> <p>*P* document published prior to the international filing date but later than the priority date claimed</p> <p>*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>*&* document member of the same patent family</p>					
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2005/000645

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98/51231 A (NOBEL BIOCARE AB; LARSSON, CECILIA; THOMSEN, PETER) 19 November 1998 (1998-11-19) page 3, line 14 - line 23 page 23, line 6 - line 9 page 28, line 33 - line 34 page 29, line 1 - line 9 -----	1-3
A	WO 02/096475 A (MEDITEAM DENTAL AB; SUL, YOUNG-TAEG) 5 December 2002 (2002-12-05) page 3, line 4 - line 12; claims -----	1-3
A	WO 03/003938 A (NOBEL BIOCARE AB ; HALL, JAN) 16 January 2003 (2003-01-16) page 7, line 25 - line 30 -----	1-3

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int'l Application No
PCT/GB2005/000645

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 03089023	A 30-10-2003	AU 2003219297 A1 CA 2473600 A1 EP 1494729 A1 WO 03089023 A1 US 2005119743 A1		03-11-2003 30-10-2003 12-01-2005 30-10-2003 02-06-2005
WO 0072777	A 07-12-2000	SE 514323 C2 AU 779521 B2 AU 5260900 A CA 2373934 A1 EP 1196110 A1 JP 2003500160 T WO 0072777 A1 SE 9901971 A		12-02-2001 27-01-2005 18-12-2000 07-12-2000 17-04-2002 07-01-2003 07-12-2000 01-12-2000
WO 9851231	A 19-11-1998	SE 513481 C2 AU 751472 B2 AU 7464298 A CA 2289627 A1 EP 0984735 A1 JP 2002511782 T SE 9701872 A WO 9851231 A1 US 6689170 B1 US 2005031663 A1		18-09-2000 15-08-2002 08-12-1998 19-11-1998 15-03-2000 16-04-2002 07-01-1999 19-11-1998 10-02-2004 10-02-2005
WO 02096475	A 05-12-2002	SE 519600 C2 EP 1397168 A1 JP 2005508862 T SE 0104213 A WO 02096475 A1 US 2004149586 A1		18-03-2003 17-03-2004 07-04-2005 30-11-2002 05-12-2002 05-08-2004
WO 03003938	A 16-01-2003	SE 519565 C2 EP 1406553 A1 SE 0102390 A WO 03003938 A1 US 2005010229 A1		11-03-2003 14-04-2004 05-01-2003 16-01-2003 13-01-2005